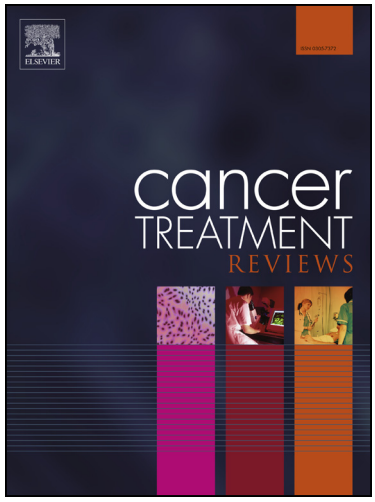
Second-line single-agent chemotherapy in human epidermal growth factor receptor 2-negative metastatic breast cancer

Puglisi, Fabio; Rea, Daniel; Kroes, Michel A.; Pronzato, Paolo

DOI:
10.1016/j.ctrv.2015.11.012

Document Version
Peer reviewed version

Citation for published version (Harvard):
Puglisi, F, Rea, D, Kroes, MA & Pronzato, P 2016, 'Second-line single-agent chemotherapy in human epidermal growth factor receptor 2-negative metastatic breast cancer: a systematic review', Cancer Treatment Reviews, vol. 43, pp. 36-49. https://doi.org/10.1016/j.ctrv.2015.11.012



Systematic or Meta-analysis Studies

Second-line single-agent chemotherapy in human epidermal growth factor receptor 2-negative metastatic breast cancer: A systematic review

Fabio Puglisi, Daniel Rea, Michel A. Kroes, Paolo Pronzato

PII: S0305-7372(15)00231-5
DOI: http://dx.doi.org/10.1016/j.ctrv.2015.11.012
Reference: YCTRV 1463

To appear in: *Cancer Treatment Reviews Cancer Treatment Reviews*

Received Date: 19 August 2015
Revised Date: 26 November 2015
Accepted Date: 30 November 2015

Please cite this article as: Puglisi, F., Rea, D., Kroes, M.A., Pronzato, P., Second-line single-agent chemotherapy in human epidermal growth factor receptor 2-negative metastatic breast cancer: A systematic review, *Cancer Treatment Reviews Cancer Treatment Reviews* (2015), doi: http://dx.doi.org/10.1016/j.ctrv.2015.11.012

TITLE PAGE

Title:

Second-line single-agent chemotherapy in human epidermal growth factor receptor 2-negative metastatic breast cancer: a systematic review

Author names and affiliations:

Prof Fabio Puglisi[a], Dr Daniel Rea[b], Michel A. Kroes[c], Prof Paolo Pronzato[d]

[a]Department of Oncology, University Hospital of Udine, Piazzale S. Maria della Misericordia, n.15, 33100, Udine, Italy; fabio.puglisi@uniud.it

[b]Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK; d.w.rea@bham.ac.uk

[c]DRG Abacus, Unit 6, Talisman Business Centre, Talisman Road, Bicester, Oxfordshire, OX26 6HR, UK; mkroes@dresourcesgroup.com

[d]IRCCS Azienda Ospedaliera Universitaria San Martino – IST, Largo Rosanna Benzi, 10, 16132, Genova, Italy; paolo.pronzato@hsanmartino.it

Corresponding Author:

Michel A. Kroes

Address: DRG Abacus, Unit 6, Talisman Business Centre, Talisman Road, Bicester, Oxfordshire, OX26 6HR, UK

Email: mkroes@dresourcesgroup.com

SECOND TITLE PAGE

Title:

Second-line single-agent chemotherapy in human epidermal growth factor receptor 2-negative metastatic breast cancer: a systematic review

Abstract

Background: No 'gold standard' exists for single-agent chemotherapy of human epidermal growth factor receptor 2-negative (HER2-negative) metastatic breast cancer (MBC) in the second-line. The objective of this systematic review is to identify and appraise overall survival (OS), progression-free survival (PFS), time to progression (TTP) and Grade III+ adverse event evidence for single-agent chemotherapy in this setting.

Methods: MEDLINE, Embase and the Cochrane Library were searched to October 2013, and PubMed October 2013 to November 2014. Electronic database searches were supplemented with hand searching of reference lists and conferences. Eligible randomised controlled trials (RCTs) employed at least one single-agent chemotherapy treatment, enrolled HER2-negative or unselected MBC patients who had progressed following first-line chemotherapy within the metastatic setting, and reported outcomes of interest for the second-line setting.

Results: Fifty-three RCTs were included in total, with most containing mixed populations by HER2 status and treatment line. Fourteen studies reported data specifically for second- and later-line treatment within the metastatic setting. Median overall survival (OS) in most trials was 8–13 months. Only one trial reported a significant difference between studied interventions in the second-line metastatic setting: nab-paclitaxel (n=131) conferred a statistically significant OS advantage vs three-weekly paclitaxel (n=136) (median OS 13.0 vs 10.7 months, respectively; hazard ratio 0.73, p=0.024) and improved overall safety.

Conclusion: One RCT demonstrated significant benefit in this setting in confirmed HER2-negative MBC alongside favourable safety. Treatment line terminology was imprecise. To reliably inform patient treatment decisions, quality-of-life data are needed and precise OS estimation according to underlying patient characteristics.

Key words: Second-line; HER2-negative; metastatic breast cancer; monotherapy; systematic review; randomised controlled trials

Introduction

Breast cancer is the most commonly diagnosed cancer and a leading cause of cancer mortality in women in both developed and developing countries. The World Health Organization estimates that more than 508,000 women died of breast cancer in 2011 [1]. Approximately 5–10% of women have metastatic breast cancer (MBC) at diagnosis [2], while a further 20–40% of breast cancer patients will go on to develop MBC [3]. MBC is an incurable disease with a median survival of 2–3 years [4-6]. Therefore, the aims of treatment are palliative: to control symptoms in order to maintain and improve patient quality of life (QoL) and, where possible, prolong survival [4].

MBC is a highly heterogeneous disease varying in tumour presentation and in biological and clinical behaviour. There are several molecular subtypes of MBC. Tumours may vary by hormone receptor status (i.e. oestrogen receptor [ER] and progesterone receptor [PR] status) and human epidermal growth factor receptor 2 [HER2] status [7]. Approximately two-thirds of breast cancer tumours express ER and/or PR receptors [8]. Hormone receptor positive tumours can be further sub-divided into luminal A and luminal B molecular subtypes, with luminal B tumours having a poorer prognosis (median survival 30 vs 45 months) [6, 9]. Treatment options include hormonal therapies and selective oestrogen receptor modulators [8]. About 15–20% of newly diagnosed breast cancers over-express HER2 (HER2+) [10-12]. These patients are treated with HER2-targeting agents (e.g. trastuzumab), in combination with hormonal therapy and/or chemotherapy [10-12]. HER2-targeting therapies have been shown to improve survival in patients with MBC [10]. In patients who are HER2-negative, but hormone receptor positive with no extensive and/or symptomatic visceral disease, hormone therapy is the first-line treatment option. In those patients with visceral involvement, chemotherapy is usually the treatment of choice [2, 13]. Triple-negative tumours do not express ER, PR and HER2, and for these patients chemotherapy is the main treatment option. According to European Society of Medical Oncology (ESMO) guidelines, there are no standard approaches for triple-negative patients requiring second- or later-line chemotherapy [2]. Beyond the use of HER2 and hormone receptor status to guide treatment, there is currently limited progress. The use of molecular profiles to select appropriate treatment options is the subject of intense research and has great potential, but is likely to be sensitive

to the emerging plethora of targeted therapies. Chemotherapy options include anthracyclines (e.g. doxorubicin, epirubicin), taxanes (e.g. docetaxel, nab-paclitaxel, and paclitaxel), vinca alkaloids (e.g. vinorelbine), anti-metabolites (e.g. capecitabine), platinum agents (e.g. cisplatin and carboplatin) and eribulin.

Treatment options for patients with MBC are dependent on several factors including disease burden, earlier treatments, response to and time elapsing since last exposure to earlier therapies, and patient characteristics and preferences [2, 13, 14]. Due to the heterogeneity of the disease, an individualised approach to the treatment of MBC is considered necessary. Following the failure of first-line therapy for MBC, the chance of response to subsequent therapy is reduced by approximately 50% with each previous regimen received [14]. However, due to the lack of predictive factors for specific agents, in some cases it is possible to see a larger than expected therapeutic benefit in second-line and/or further lines of therapy. Single-agent chemotherapy is the preferred treatment option in patients without severely symptomatic or immediately life-threatening disease [2]. In addition, treatment options in the second- and later-line settings are often limited by drug resistance as a result of earlier exposure to cytotoxic regimens [15]. For example, patients receiving second-line treatment for MBC will often have previously received a taxane and/or anthracycline-based chemotherapy, which may subsequently result in treatment-resistant cases of MBC.

At present there is no ‘gold standard’ of treatment for MBC [14]. Physicians must rely on clinical trial data to make decisions regarding the most beneficial course of treatment for patients following first-line therapy failure [15]. In this respect, well-designed, objective, randomised controlled trials (RCTs) are fundamental to informing clinical practice. However, the majority of trials tend to focus on the comparison of specific treatments in pre-defined patient populations at a specific phase of disease, and also have relatively short follow-up periods, producing MBC populations that are not representative of those seen in clinical practice [16]. There is therefore a need for physicians to understand the current evidence base for single-agent therapy for HER2-negative MBC second-line treatment.

The present systematic review (SR) was conducted in order to qualitatively synthesise the evidence base for the treatment of MBC and to make recommendations regarding future trials in this setting.

Methods

Search strategy

The present SR was performed in accordance with Cochrane recommendations [17]. A pre-defined SR protocol was produced. The original SR searches were run in the electronic databases of MEDLINE, Embase and The Cochrane Library on 17th September 2012. A subsequent update search in these databases was conducted on 30th October 2013. A further update was performed in PubMed for the period 30th October 2013 to 14th November 2014.

Additionally, the following sources were hand searched: reference lists of included RCTs; studies included in relevant SRs; clinical trials databases; and National Institute for Health and Care Excellence (NICE) technology appraisals, evidence reviews and clinical guidelines relating to chemotherapy treatment in patients with advanced or metastatic breast cancer. The following conference proceedings (2010–2013 inclusive) were searched for trial data without full publications: American Society of Clinical Oncology (ASCO); European Cancer Organisation (ECCO); European Society of Medical Oncology (ESMO); International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

Eligible studies were Phase II or Phase III RCTs. Studies meeting the inclusion criteria were RCTs that had enrolled patients to receive single-agent chemotherapy as a second-line treatment for HER2-negative advanced or metastatic breast cancer. 'Second-line' was defined as patients who had received one prior line of chemotherapy treatment in the advanced or metastatic setting. It was anticipated that RCTs would be retrieved that contained 'mixed-lines' (i.e. combined results for patients treated at first-, second- or third-line, etc.); therefore, any studies containing second-line treated patients were included, and the proportions of second-line treated patients noted. It was also anticipated that some trials would pre-date the period from which HER2 testing began in clinical practice. Therefore, the SR included studies where HER2 status of enrolled patients was not reported,

as it anticipated that such studies would contain patients who were HER2-negative (albeit at an unknown proportion). Trials of exclusively HER2+ patients and of patients who were naïve to chemotherapy treatment were excluded.

Comparators

The single-agent comparators for the treatment of MBC included in the SR were: taxanes (paclitaxel, nab-paclitaxel, docetaxel), vinca alkaloids (vinorelbine, vinblastine, vincristine), platinum-based treatments (cisplatin, carboplatin), anthracyclines (doxorubicin, pegylated liposomal doxorubicin [PLD], epirubicin) and other monotherapy (capecitabine, gemcitabine, eribulin, melphelan or cyclophosphamide) vs any comparator. Nab-paclitaxel is licensed in MBC patients for whom anthracyclines are not suitable, so the anthracyclines included here, doxorubicin, PLD and epirubicin, would not be direct comparators, but are included as they may still be used in second-line therapy.

Topoisomerase inhibitors were not included; amrubicin as it is unlicensed in MBC, and irinotecan because it is unlicensed in breast cancer. Also excluded were hormonal treatments (aromatase inhibitors), marimastat (due to its development having been terminated), tyrosine kinase inhibitors (lapatinib, reatinib, afatinib, BMS-754807, sunitinib, pazopanib, dasatinib) and inhibitors of downstream targets (everolimus, BKM120, BEZ-235, tanespimycin, retaspimycin, AUY922).

Outcome measures

The SR focused on the following efficacy outcomes: overall survival (OS), progression free survival (PFS), and time to progression (TTP). Data for QoL and other patient-reported outcomes were also sought. The following toxicity outcomes were included: withdrawal from treatment due to toxicity, haematological adverse events (AEs), non-haematological AEs, Grade three and four AEs, and mortality.

Data collection

A reviewer conducted the database searches and screening of citation abstracts for inclusion, according to a pre-defined SR protocol. Following abstract screening, full publications of potentially

includable studies were retrieved for further review against the protocol eligibility criteria. Inclusion/exclusion of citations was verified by another reviewer. Any disputes regarding eligibility were referred to a third reviewer. Study methodology, patient characteristics, and clinical outcomes data of included studies were extracted into a pre-determined data extraction table produced using Microsoft Excel®. Quality appraisal of the elements of selection, attrition, detection, and performance bias was performed in accordance with the NICE Guidelines Manual 2009 [18], which assesses risk of bias at the study level.

Results

A PRISMA flow diagram of the citation screening for the original and updated SRs is shown in Figure 1. The original electronic database searches identified a total of 15,356 potentially relevant publications, of which 4,285 duplicates were excluded. Subsequently, 11,071 citations were screened on the basis of title and abstract. A further 10,979 citations were excluded, leaving 92 citations, the full publications of which were acquired. Upon reapplication of the eligibility criteria, a further 49 citations were excluded, and one citation was included from hand searching. Therefore, the original SR identified 44 publications reporting on 43 individual RCTs. The first SR update yielded seven further included RCTs; and the PubMed update another three RCTs. Therefore, a total of 53 RCTs were included, of which 14 reported data specifically for second- and/or later-line treatment within the metastatic setting.

Study and patient level characteristics of trials enrolling second- and/or later-line patients (n=14)

Table 1 categorises included RCTs by treatment line, including key trial characteristics. Of the 14 second- and/or later-line papers, five [19-23] reported data for a purely second-line patient population, three [24-26] reported data from mixed-line treatment but provided results for the second-line subgroup separately, three [27-29] had unclear second-line status (i.e. it was unclear whether the previous therapy had been given in the adjuvant or metastatic setting), two [30, 31] reported data from second- or later-line patients, and one [32] reported data from a second- or later-line subgroup

separately. The categorisation of the other 39 RCTs as first- or later-line (mixed) patients has been tabulated (data not shown, available on request).

There were five phase II trials, seven phase III and two trials did not report the phase. Considering sample size, the greater weight of evidence for effects in second- and/or later-line therapy comes from the recent TANIA trial (von Minckwitz et al, 2014; N=494) [19]; Gradishar et al, 2005 (N=268) [32]; Keller et al, 2004 (N=301) [31]; and Joensuu et al, 1998 (N=162) [26].

Only three trials enrolled confirmed HER2-negative patients specifically [19, 27, 29]. Papadimitriou et al, 2009 [23] enrolled unselected patients reporting that 21–24% were HER2+, 29–34% HER2-negative, and 34–42% of unknown HER2 status. Palmieri et al, 2012 [30] also enrolled unselected patients but did not report their HER2 status. The other nine trials did not report HER2 status [20-22, 24-26, 28, 31, 32].

An overview of the patient characteristics across treatment arms is shown in Table 2. *Within* trials, there were some potential imbalances between treatment arms: the proportion of patients with oestrogen or progesterone receptor positivity (ER+ and/or PR+) in Baselga et al, 2012 [29] was numerically higher on sorafenib + capecitabine vs capecitabine; the proportion ER+ in Venturino et al, 2000 [20] was higher in the vinorelbine monotherapy arm; the proportion of patients with ECOG (Eastern Cooperative Oncology Group) status 0 was higher with docetaxel monotherapy vs docetaxel + gemcitabine in Papadimitriou et al, 2009 [23]; median ECOG status was lower in the vinorelbine monotherapy arm and the proportion of patients with visceral metastases also lower in Venturino et al, 2000 [20]; the proportion of patients with visceral metastases was numerically higher on mitomycin vs paclitaxel in Dieras et al, 1995 [21]; and median age was slightly higher in the epirubicin arm vs doxorubicin in Gasparini et al, 1991 [22].

There was much variation *between* trials with regards to the proportion of patients with visceral metastases, (Table 2): from 38% in Gasparini et al, 1991 [22] to 95% in Dieras et al, 1995 [21] for any visceral metastases; from 19–61% for liver metastases; and 26–61% for lung metastases. There was also considerable variation in the number of metastatic disease sites. Hormone receptor status also

varied across trials, ER positivity ranging from 30–56%, and PR positivity from 5.6–30%, where reported.

Outcomes reported

The primary endpoint was OS in two trials [26, 30], PFS in four [19, 27, 29, 31], overall response in three [23, 28, 32] and not reported in five papers published between 1990 and 2000 [20-22, 24, 25] (Table 1). Safety/toxicity was typically a secondary endpoint, amongst others. Only three papers examined QoL as an endpoint: one from Canada [24] provided QLQ-C30 data, one [26] in Finland used the Rotterdam Symptom Checklist and the recent, mainly European, TANIA trial [19] did not report the patient-reported outcome (PRO) data in the 2014 paper, the authors stating that PRO data would be reported separately, as would the final OS analysis and third-line PFS and third-line safety after further follow-up of trial patients. Neither Norris et al, 2000 [24] nor Joensuu et al, 1998 [26] reported the QoL data separately for the second-line subgroup.

Overall survival in second- and later-line setting

Median OS according to treatment line is shown in Table 3 and Table 4; 12 of 14 trials reported OS. Ahmad et al, 2013 [28] did not report OS and in Sato et al, 2012 [27] and von Minckwtiz et al, 2014 [19] median OS had not been reached, i.e. the OS data were immature. Only one trial demonstrated a statistically significant difference in OS in the second- and later-line setting: nab-paclitaxel demonstrated significantly longer median OS compared with standard paclitaxel 175mg/m^2 every 3 weeks (q3w) (13.0 vs 10.7 months, respectively; hazard ratio [HR] 0.73, p=0.024) in a large (n=268) phase III multinational trial performed in USA/Canada, UK and Russia/Ukraine [32].

In the majority of second-line trials, median survival was from 8–13 months. Absolute survival was, however, much longer in the monotherapy arm of Papadimitriou et al, 2009 [23], with median OS 28 months (95% CI: 15.7, 40.3) on weekly docetaxel (DTX) 40mg/m^2 vs 14 months (95% CI: 3, 25) on weekly DTX 35mg/m^2 + gemcitabine, in spite of the actual median relative dose intensity of docetaxel being 0.6 and that of gemcitabine being 0.5. These results should be viewed with caution, however, as the trial was relatively small (n=88). The higher proportion of patients with ECOG status

0 in the DTX monotherapy arm (71%) compared with the combination arm (56%) may have contributed to the longer duration of OS in the monotherapy arm (28 months). The fact that the HER2+ patients in this trial also received trastuzumab may have contributed positively to the overall OS length in both arms. Median OS was also long in the trial of Baselga et al, 2012 [29], where the reportedly second-line subgroup patients had median OS of 23.4 months on capecitabine and 19 months on capecitabine + sorafenib. The reporting is not clear, however, as to whether second-line relates to chemotherapy overall or to the setting within metastatic disease. It may therefore be that this subgroup includes patients that were in the first-line metastatic setting. This trial also had a high proportion of patients with ECOG status 0 (68.7% in the sorafenib + capecitabine arm and 67.5% in the placebo + capecitabine arm) (Table 2) and only enrolled HER2-negative patients (so did not have HER2+ patients without trastuzumab treatment). Absolute OS was particularly low in the small (n=37) UK phase II trial of Palmieri et al, 2012 [30] on DTX 100mg/m^2 weekly (median OS 7.8 months, 95% CI: 4.8, 11) and on vinorelbine (median 4.9 months, 95% CI: 3.9, 5.8). This may have been due in part to more than 80% of patients being third- or later-line within the metastatic setting, all patients being anthracycline-resistant and also to patients' HER2 status being unknown. Although this study had OS as a primary objective, no statistically significant difference was observed between the arms, although this may have been influenced by the small sample size and extensive crossover at progression.

There was no OS data for weekly paclitaxel (PTX), and the majority of papers unfortunately did not report the 95% confidence interval around the median OS estimate. No RCT used modern adjustment methods to account for crossover of patients from the control arm, such as Rank Preserving Structural Failure Time (RPSFT) or Inverse Probability Censoring Weighted (IPCW) analyses [33].

Progression-free survival in second- and later-line setting

Median PFS was reported in four trials [19, 27, 29, 31, 34]. Three trials demonstrated significantly longer PFS: capecitabine + sorafenib (6.4 months) vs capecitabine (4.1 months), HR 0.58 (95% CI: 0.41, 0.81), p=0.001 [29]; capecitabine + low dose DTX (10.5 months) vs DTX monotherapy before

having sequential capecitabine (9.8 months), HR 0.62 (95% CI: 0.40, 0.97), p=0.0342 [27]; bevacizumab + chemotherapy (6.3 months, 95% CI: 5.4, 7.2) vs single-agent treatment of physician's choice (TPC) (approx. 60% capecitabine) (4.2 months, 95% CI: 3.9, 4.7), HR 0.75 (95% CI: 0.61, 0.93), p=0.0068 [19].

In Keller et al, 2004 [31] pegylated liposomal doxorubicin showed no benefit over control therapy of either vinorelbine or mitomycin C + vinblastine (PFS 2.9 and 2.5 months, respectively; HR 1.26 (95% CI: 0.98, 1.62); p=0.11 [31].

Time to progression

Of seven trials reporting TTP, three showed a significantly longer TTP: 3-weekly paclitaxel showed benefit over mitomycin (median TTP 3.5 vs 1.6 months, respectively; p=0.026) [21]; capecitabine + sorafenib was superior to capecitabine alone (median TTP 6.8 vs 4.1 months, respectively; HR 0.56 [95% CI: 0.39, 0.8]; p=0.001) [29]; and nab-paclitaxel was associated with significantly greater TTP vs standard paclitaxel q3w (median TTP 4.8 vs 3.7 months, respectively; HR 0.73; p=0.02) [32].

No benefit in terms of TTP was demonstrated for doxorubicin + vinorelbine vs doxorubicin monotherapy (TTP 4.3 vs 5.3 months, respectively) [24], for pegylated liposomal doxorubicin vs vinorelbine or mitomycin C + vinblastine (p>0.05) [31], for 3-weekly docetaxel vs vinorelbine (2.4 vs 1.7 months, respectively; p=0.82) [30], or for epirubicin vs epirubicin + vindesine (TTP 6 months in both treatment arms) [25].

Grade III+ adverse events, discontinuation and safety summary

An overview of key safety results is shown in Table 5. Of the treatments or treatment combinations showing significant efficacy benefit, the only treatment with a demonstrated better overall safety profile was nab-paclitaxel vs 3-weekly standard paclitaxel [32]: although grade III sensory neuropathy occurred more frequently with nab-paclitaxel (10% vs 2%, respectively), treatment-related grade IV neutropenia was significantly lower on nab-paclitaxel (9% vs 22%, p<0.001), there were no grade III/IV hypersensitivity reactions with nab-paclitaxel (despite being no premedication in this arm)

whereas there were such reactions with standard paclitaxel (with premedication given), and AE-related discontinuations and dose reductions or delays were low in both arms (3% with nab-paclitaxel and 7% on standard paclitaxel), as was febrile neutropenia (<2% in both arms).

Low-dose (60mg/m^2) docetaxel + capecitabine concomitantly, which had shown a PFS benefit vs docetaxel 70mg/m^2 (prior to sequential capecitabine) showed non-significantly reduced haematological AEs, higher frequency of hand-foot syndrome (7.4% vs 0%, respectively) and lower frequencies of fatigue and peripheral oedema (Table 5) [27]. Paclitaxel 3qw had shown increased TTP vs mitomycin, but the safety profile was difficult to interpret because although taxane therapy was associated with more frequent grade III/IV neutropenia & peripheral neuropathy, patients received substantially more courses of PTX than mitomycin [21]. Thrombocytopenia was more common with mitomycin [21]. Sorafenib added to capecitabine had shown increased TTP and PFS, but was associated with a significantly higher frequency of grade III/IV hand-foot syndrome (44% vs 14% with monotherapy capecitabine) and discontinuation due to AEs (mainly hand-foot syndrome and diarrhoea) were higher also (20% vs 9%, respectively) [29]. The addition of bevacizumab to (mainly) capecitabine was beneficial to PFS, yet Grade III/IV AEs were more common with the combination treatment, mainly due to higher incidences of grade III hypertension and proteinuria. Discontinuation was also higher with the combination (Table 5) [19].

Risk of bias assessment of second- and later-line trials (n=14)

Of the 14 RCTs, 13 were full papers and so could be assessed for quality. Seven reported efficacy data on an intention-to-treat basis [19, 24, 25, 29, 31, 32, 34], randomisation was carried out appropriately in five [19, 22, 24, 26, 29, 34], but concealment of treatment allocation was unclear in most trials. Only one trial was double-blinded [29] and almost all trials did not have blinded outcome assessors. In terms of the distribution of patient characteristics between treatment groups, slight imbalances in potential prognostic factors were noted in six trials [20-24, 29]. Few trials reported confidence intervals around point estimates and only three confirmed HER2-negative status at

enrolment. No trial assessed or commented on discordant HER2 status between the primary tumour and metastases.

Discussion

To the best of our knowledge, this is the first SR to have been conducted to identify RCT evidence for the single-agent treatment of HER2-negative MBC at the second-line stage. Limited data are available for this setting: commercial sponsors are not enthusiastic; the market diminishes in size; and measurable outcomes are small. In addition, there is a clinical heterogeneity that accumulates due to prior treatment, performance status, and patient preferences. Only 14 trials reported data separately or were exclusively conducted in the second- or later-line setting.

OS has long been regarded as the 'gold standard' measurement of clinical benefit in RCTs and is considered the primary measure of benefit in oncology [35]. Improvement in median OS is also considered an important outcome to determine clinical benefit of a new treatment compared with standard-of-care in the ASCO value framework proposed for advanced disease [36]. OS advantage is not easily demonstrable in this setting as the majority of RCTs are not usually sufficiently powered to detect OS benefits [37], longer follow-up is required [35], and estimates can be influenced by subsequent treatments once a particular trial has ended [37], details of which may not have been collected and reported.

Of five trials demonstrating efficacy benefit (OS, PFS and/or TTP), only one showed significantly increased OS: nab-paclitaxel vs standard paclitaxel in the second- and later-line setting [32]. The survival benefit with nab-paclitaxel was realised with significantly less treatment-related grade IV neutropenia, and low levels of febrile neutropenia and AE-related discontinuation. The mature OS data from TANIA [19], examining the addition of bevacizumab to single-agent chemotherapy, are awaited. Much of the variation in absolute OS estimates can be explained by differences in the characteristics of enrolled patients, including ECOG status, crossover effects (not adjusted for) and whether second- or third-line patients were enrolled.

All of the larger trials had good aspects of quality, including intention-to-treat analysis. Although all were open-label, concealment of treatment allocation was largely not detailed and outcome assessors were not blinded. In two of the trials [31, 32], the randomisation method was not fully detailed, in that the sequence generation was not discussed. However both studies used stratification and there was no evidence of any imbalance between the treatment arms.

As physicians rely on RCT data when deciding the most appropriate treatment for MBC patients failing first-line therapy [15], there is a need for high-quality RCT evidence specifically in the second-line treatment of HER2-negative MBC patients, including OS estimation with adjustment for crossover effects [33], QoL estimation, and an understanding of patient preferences at this stage (whether the highest efficacy is of primary concern or whether the better safety profile of a single-agent therapy is preferred).

Two recent reviews in MBC have been published, Palumbo et al, 2013 [16] and Partridge et al, 2014 [38], the latter providing the basis for the latest ASCO clinical practice guideline for 'Chemo- and targeted therapy for women with HER2-negative (or unknown) advanced breast cancer' [39]. In this study, the search strategy was limited to publications from 1993 onwards and did not include searching of the electronic database Embase; therefore this SR did not identify nine studies [20-26, 30, 32], and most notably Gradishar et al. 2005 [32], demonstrating statistically significant OS benefit for nab-paclitaxel vs paclitaxel, was omitted from the ASCO guidelines [39]. Also not searched was PubMed for e-publications ahead of print, which identified the TANIA trial [19] in our SR.

In Palumbo 2013, the search strategy is not detailed. Of the 14 trials we identified, Palumbo identified four [24, 26, 31, 32].

We did not include the IMELDA trial (Gligorov et al, 2014 [40]) as it focuses on maintenance of first-line metastatic treatment response (i.e. progression-free patients), rather than on treating patients who have failed first-line metastatic treatment. The different nature of the patient population is reflected in the median OS values in the two treatment arms of 39.0 months on bevacizumab + capecitabine and 23.7 months on bevacizumab alone. Further, we did not include Guan et al, 2009 [41] as the only data

reported specifically for the second- and later-line subgroup (n=85) was the clinical benefit rate, which was 51% with nab-paclitaxel (n=43) and 33% with standard paclitaxel (n=42), p=0.181. Outcomes of interest (OS, PFS, TTP and safety) were not reported for the second- or later-line subgroup.

Classification of the line of therapy also appeared to be defined differently in these reviews than in our SR. Partridge et al, 2014 [38] included two studies as second-line; Cortes et al, 2011 [34] that was excluded from our SR because it enrolled patients with 2-5 prior chemotherapy treatments with two or more prior regimens for advanced disease and therefore represented a third- or later-line setting, and Keller et al, 2004 [31] that we classified as 'second- or later-line' because it enrolled patients with 'no more than two chemotherapy regimens in the advanced setting (excluding adjuvant setting)' and so would have included some third-line patients. Two other studies [27, 29], were classified as second-line, whereas we classified these as uncertain second-line therapy as it was unclear if the second-line label related to chemotherapies or to the setting within metastatic disease. In Palumbo et al, 2013 [16], the line of therapy is seemingly classified according to the number of lines overall rather than by the number of lines within metastatic disease, meaning that the trials included are of a more heterogeneous nature than in our SR, as they will include trials with some patients who are first-line in the MBC setting. These distinctions are of importance as they help to better explain the OS and PFS data observed and, if papers provide not only median estimates but also the 95% confidence interval, then clinicians and patients will have more informative data on progression after failure of first-line treatment of metastatic disease upon which to base their treatment decision.

One limitation to the methods employed in this SR is that, due to time constraints, we were only able to perform the second search update from October 2013 in PubMed, rather than conducting it in all the electronic databases. Comparison of outcomes between trials was hampered by the lack of common comparators across the evidence base, many of the single-agent therapies being compared with combination treatments, and heterogeneity (beyond line of therapy) being contributed further to by potential differential assignment of patients to trials, e.g. patients enrolled in capecitabine trials may, in general, have a lower disease burden than those in vinorelbine trials, varying chemotherapy

exposure (e.g. per-protocol maximum number of cycles and the dose reduction criteria applied to manage toxicity events), and varying schedule and cumulative dose across a cycle (e.g. the cumulative dose of a taxane administered across a cycle is known to predict neurotoxicity, with the 3-weekly schedule having a lower cumulative dose than weekly administration [42]). There was a distinct lack of QoL data that, in this setting, is a data gap, critical to be filled if clinical practice and patient decision-making is to be fully informed as well as reimbursement obtained [43].

Conclusion

There are few RCTs conducted specifically in the second-line HER2-negative MBC setting. Nab-paclitaxel was the only single agent that demonstrated a survival advantage at the second-line and beyond. Few treatment options provide clinical benefit without adversely influencing tolerability. Given that MBC is an incurable disease and that an equally important aim of treatment at this stage is to enhance QoL and enable patients to be at home with their families, it is vital that trial investigators and clinicians set standards for the design and conduct of clinical trials with this aim in mind, with patients enrolled according to the treatment line received within the metastatic setting, with sufficient sample size to enable outcomes to be estimated with greater precision, with HER2-negative status and any discordant status established, a non-invasive method that has recently been tested in phase I [44], and with PROs recorded. This would contribute to physicians being able to more reliably inform patients regarding the likely range of treatment outcomes, and thereby help patients reach the treatment decision that is right for them.

Conflict of interest

Celgene International Sàrl, Switzerland funded Abacus International, UK in the conduct of the present systematic review, and was involved in the study design and decision to publish the present systematic review. The co-authors Fabio Puglisi, Daniel Rea and Paolo Pronzato received honoraria for their participation in the systematic review or manuscript. Michel A. Kroes is an employee of DRG Abacus. Fabio Puglisi received honoraria for consultancies to Celgene, Eisai, Novartis and

Roche. Daniel Rea received research funding from Celgene. Paolo Pronzato was a speaker at meetings or advisory boards for Celgene, Eisai, Genomics Health, Hospira, Novartis and Roche.

Contributors

The co-authors Fabio Puglisi, Daniel Rea and Paolo Pronzato have contributed to the study design and data interpretation of the systematic review, and the drafting of the manuscript. Michel A. Kroes has contributed to data interpretation of the systematic review, and drafting of the manuscript. All authors have approved the final article.

Acknowledgements

This systematic review and manuscript development were funded by Celgene International Sàrl, Switzerland.

The authors thank Ajay S. Patel and Katherine S. MacGilchrist for their contributions in conducting the systematic review and writing the manuscript whilst in the employment of Abacus International and Andrea Ditchfield (Abacus International) for assistance in writing the article.

References

[1]. World Health Organization. Breast cancer: prevention and control. Breast cancer burden. Available from: www.who.int/cancer/detection/breastcancer/en/index1.html (accessed 12 June 2015).

[2]. Cardoso F, Harbeck N, Fallowfield L, Kyriakides S, Senkus E. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012 Oct;23 Suppl 7:vii11-9.

[3]. Vera-Llonch M, Weycker D, Glass A, Gao S, Borker R, Qin A, et al. Healthcare costs in women with metastatic breast cancer receiving chemotherapy as their principal treatment modality. BMC Cancer. 2011;11:250.

[4]. Lin NU, Thomssen C, Cardoso F, Cameron D, Cufer T, Fallowfield L, et al. International guidelines for management of metastatic breast cancer (MBC) from the European School of Oncology (ESO)-MBC Task Force: Surveillance, staging, and evaluation of patients with early-stage and metastatic breast cancer. Breast. 2013 Jun;22(3):203-10.

[5]. Kiely BE, Soon YY, Tattersall MH, Stockler MR. How long have I got? Estimating typical, best-case, and worst-case scenarios for patients starting first-line chemotherapy for metastatic breast cancer: a systematic review of recent randomized trials. J Clin Oncol. 2011 Feb 1;29(4):456-63.

[6]. Bonotto M, Gerratana L, Poletto E, Driol P, Giangreco M, Russo S, et al. Measures of outcome in metastatic breast cancer: insights from a real-world scenario. Oncologist. 2014 Jun;19(6):608-15.

[7]. Vuong D, Simpson PT, Green B, Cummings MC, Lakhani SR. Molecular classification of breast cancer. Virchows Arch. 2014 Jul;465(1):1-14.

[8]. Burstein HJ, Temin S, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: american society of clinical oncology clinical practice guideline focused update. J Clin Oncol. 2014 Jul 20;32(21):2255-69.

[9]. Cheang MC, Chia SK, Voduc D, Gao D, Leung S, Snider J, et al. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. J Natl Cancer Inst. 2009 May 20;101(10):736-50.

[10]. Giordano SH, Temin S, Kirshner JJ, Chandarlapaty S, Crews JR, Davidson NE, et al. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: american society of clinical oncology clinical practice guideline. J Clin Oncol. 2014 Jul 1;32(19):2078-99.

[11]. Puglisi F, Minisini AM, De Angelis C, Arpino G. Overcoming treatment resistance in HER2-positive breast cancer: potential strategies. Drugs. 2012 Jun 18;72(9):1175-93.

[12]. Arteaga CL, Sliwkowski MX, Osborne CK, Perez EA, Puglisi F, Gianni L. Treatment of HER2-positive breast cancer: current status and future perspectives. Nature Reviews Clinical Oncology. 2012 Jan;9(1):16-32.

[13]. Andreetta C, Minisini AM, Miscoria M, Puglisi F. First-line chemotherapy with or without biologic agents for metastatic breast cancer. Critical Reviews in Oncology-Hematology. 2010 Nov;76(2):99-111.

[14]. Jones SE. Metastatic breast cancer: the treatment challenge. Clin Breast Cancer. 2008 Jun;8(3):224-33.

[15]. Roche H, Vahdat LT. Treatment of metastatic breast cancer: second line and beyond. Ann Oncol. 2011 May;22(5):1000-10.

[16]. Palumbo R, Sottotetti F, Riccardi A, Teragni C, Pozzi E, Quaquarini E, et al. Which patients with metastatic breast cancer benefit from subsequent lines of treatment? An update for clinicians. Ther Adv Med Oncol. 2013 Nov;5(6):334-50.

[17]. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org (Accessed 12 June 2015).

[18]. NICE Guidelines Manual 2012. Appendix C Methodology checklist: randomised controlled trials. Available at: http://publications.nice.org.uk/the-guidelines-manual-appendices-bi-pmg6b/appendix-c-methodology-checklist-randomised-controlled-trials (accessed 12 June 2015).

[19]. von Minckwitz G, Puglisi F, Cortes J, Vrdoljak E, Marschner N, Zielinski C, et al. Bevacizumab plus chemotherapy versus chemotherapy alone as second-line treatment for patients with HER2-negative locally recurrent or metastatic breast cancer after first-line treatment with bevacizumab plus chemotherapy (TANIA): an open-label, randomised phase 3 trial. Lancet Oncol. 2014 Oct;15(11):1269-78.

[20]. Venturino A, Comandini D, Simoni C, Merlini L, Naso C, Palumbo R, et al. Is salvage chemotherapy for metastatic breast cancer always effective and well tolerated? A phase II randomized trial of vinorelbine versus 5-fluorouracil plus leucovorin versus combination of mitoxantrone, 5-fluorouracil plus leucovorin. Breast cancer research and treatment. 2000;60(3):195-200.

[21]. Dieras V, Marty M, Tubiana N, Corette L, Morvan F, Serin D, et al. Phase II randomized study of paclitaxel versus mitomycin in advanced breast cancer. Seminars in oncology. 1995 Aug;22(4 Suppl 8):33-9.

[22]. Gasparini G, Dal Fior S, Panizzoni GA, Favretto S, Pozza F. Weekly epirubicin versus doxorubicin as second line therapy in advanced breast cancer. A randomized clinical trial. American journal of clinical oncology. 1991 Feb;14(1):38-44.

[23]. Papadimitriou CA, Kalofonos H, Zagouri F, Papakostas P, Bozas G, Makatsoris T, et al. Weekly docetaxel with or without gemcitabine as second-line chemotherapy in paclitaxel-pretreated patients with metastatic breast cancer: a randomized phase II study conducted by the Hellenic Co-Operative Oncology Group. Oncology. 2009;77(3-4):212-6.

[24]. Norris B, Pritchard KI, James K, Myles J, Bennett K, Marlin S, et al. Phase III comparative study of vinorelbine combined with doxorubicin versus doxorubicin alone in disseminated metastatic/recurrent breast cancer: National Cancer Institute of Canada Clinical Trials Group Study MA8. Journal of Clinical Oncology. 2000 June;18(12):2385-94.

[25]. Nielsen D, Dombernowsky P, Skovsgaard T, Jensen J, Andersen E, Engelholm SA, et al. Epirubicin or epirubicin and vindesine in advanced breast cancer. A phase III study. Annals of Oncology. 1990 Jul;1(4):275-80.

[26]. Joensuu H, Holli K, Heikkinen M, Suonio E, Aro AR, Hietanen P, et al. Combination chemotherapy versus single-agent therapy as first- and second-line treatment in metastatic breast cancer: A prospective randomized trial. Journal of Clinical Oncology. 1998 December;16(12):3720-30.

[27]. Sato N, Yamamoto D, Rai Y, Iwase H, Saito M, Iwata H, et al. Evaluation on efficacy and safety of capecitabine plus docetaxel versus docetaxel monotherapy in metastatic breast cancer patients pretreated with anthracycline: results from a randomized phase III study (JO21095). Clinical Advances in Hematology & Oncology. 2012;11(3):Supplement 4.

[28]. Ahmad A, Sheikh S, Taran R, Srivastav SP, Prasad K, Rajappa SJ, et al. Therapeutic efficacy of a novel nanosomal docetaxel lipid suspension compared with taxotere in locally advanced or metastatic breast cancer patients. Clin Breast Cancer. 2014 Jun;14(3):177-81.

[29]. Baselga J, Segalla JG, Roche H, Del Giglio A, Pinczowski H, Ciruelos EM, et al. Sorafenib in combination with capecitabine: an oral regimen for patients with HER2-negative locally advanced or metastatic breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012 1 May;30(13):1484-91.

[30]. Palmieri C, Alifrangis C, Shipway D, Tat T, Watson V, Mackie D, et al. A randomized feasibility study of docetaxel versus vinorelbine in advanced breast cancer. Oncologist. 2012;17(11):1429-e47.

[31]. Keller AM, Mennel RG, Georgoulias VA, Nabholtz JM, Erazo A, Lluch A, et al. Randomized phase III trial of pegylated liposomal doxorubicin versus vinorelbine or mitomycin C plus vinblastine in women with taxane-refractory advanced breast cancer. Journal of Clinical Oncology. 2004;22(19):3893-901.

[32]. Gradishar WJ, Tjulandin S, Davidson N, Shaw H, Desai N, Bhar P, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based

paclitaxel in women with breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2005 1 Nov;23(31):7794-803.

[33]. Ishak KJ, Proskorovsky I, Korytowsky B, Sandin R, Faivre S, Valle J. Methods for adjusting for bias due to crossover in oncology trials. Pharmacoeconomics. 2014 Jun;32(6):533-46.

[34]. Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet. 2011 Mar 12;377(9769):914-23.

[35]. US Food and Drug Administration. Guidance for industry 2007. Clinical trial endpoints for the approval of cancer drugs and biologics. Available from: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf (Accessed 12 June 2015).

[36]. Schnipper LE, Davidson NE, Wollins DS, Tyne C, Blayney DW, Blum D, et al. American Society of Clinical Oncology Statement: A Conceptual Framework to Assess the Value of Cancer Treatment Options. J Clin Oncol. 2015 Aug 10;33(23):2563-77.

[37]. Verma S, McLeod D, Batist G, Robidoux A, Martins IR, Mackey JR. In the end what matters most? A review of clinical endpoints in advanced breast cancer. Oncologist. 2011;16(1):25-35.

[38]. Partridge AH, Rumble RB, Carey LA, Come SE, Davidson NE, Di Leo A, et al. Chemotherapy and targeted therapy for women with human epidermal growth factor receptor 2-negative (or unknown) advanced breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2014 Oct 10;32(29):3307-29.

[39]. ASCO. Clinical Practice Guideline 1-17: Chemo- and Targeted Therapy for Women with HER2 Negative (or unknown) Advanced Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. 2014. Available at: http://www.asco.org/guidelines/ABC_HER2-negative_chemo (accessed 12 June 2015).

[40]. Gligorov J, Doval D, Bines J, Alba E, Cortes P, Pierga JY, et al. Maintenance capecitabine and bevacizumab versus bevacizumab alone after initial first-line bevacizumab and docetaxel for patients with HER2-negative metastatic breast cancer (IMELDA): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014 Nov;15(12):1351-60.

[41]. Guan ZZ, Li QL, Feng F, Jiang Z, Shen Z, Yu S, et al. Superior efficacy of a cremophor-free albumin-bound paclitaxel compared with solvent-based paclitaxel in chinese patients with metastatic breast cancer. Asia-Pacific Journal of Clinical Oncology. 2009 September;5(3):165-74.

[42]. Scripture CD, Figg WD, Sparreboom A. Peripheral neuropathy induced by paclitaxel: recent insights and future perspectives. Curr Neuropharmacol. 2006 Apr;4(2):165-72.

[43]. Calvert M, Brundage M, Jacobsen PB, Schunemann HJ, Efficace F. The CONSORT Patient-Reported Outcome (PRO) extension: implications for clinical trials and practice. Health & Quality of Life Outcomes. 2013 Oct 29;11(1):184.

[44]. Sorensen J, Sandberg D, Sandstrom M, Wennborg A, Feldwisch J, Tolmachev V, et al. First-in-human molecular imaging of HER2 expression in breast cancer metastases using the 111In-ABY-025 affibody molecule. Journal of Nuclear Medicine. 2014 May;55(5):730-5.

Table 1: Trial characteristics of RCTs investigating second- and/or later-line therapy for metastatic disease (n=14)

Line of therapy within metastatic setting	First author, year	Phase	N	2nd line subgroup size	Location	Enrolment criteria	HER2 status	Primary endpoint
2nd line	Gasparini, 1991	NR	49	N/A	Italy	Progressing MBC after CMF with or without endocrine therapy. No prior anthracycline permitted.	NR	NR
	Dieras, 1995	II	81	N/A	France	Progressing MBC after one (metastatic) or two (metastatic and adjuvant) chemotherapy regimens.	NR	NR
	Venturino, 2000	II	99	N/A	Italy	Progressive MBC, one previous chemotherapy for metastatic disease.	NR	NR
	Papadimitriou, 2009	II	88	N/A	Greece	MBC patients, progressed after 1st line treatment with paclitaxel in metastatic setting. If HER2+, trastuzumab added to study treatment.	21–24% HER2+, 29–34% HER2–, 34–42% unknown	ORR
	Von Minckwitz, 2014/TANIA	III	494	N/A	France, Hungary, Spain, Italy, Austria, Croatia, Germany, Switzerland, Slovakia, Greece, Israel, Argentina	Locally recurrent or MBC patients, progressed after 1st line treatment with bevacizumab + chemotherapy.	100% HER2–	PFS
2nd line (subgroup)	Nielsen 1990,	III	143	75	Denmark	Progressive ABC, with prior chemotherapy in either adjuvant or metastatic setting.	NR	NR
	Joensuu 1998,	NR	303	162	Finland	MBC patients without prior chemotherapy for metastatic disease, given either monotherapy or combination therapy in the 1st line and then monotherapy or combination therapy in the 2nd line. Results reported for OS from second line.	NR	OS
	Norris 2000,	III	303	NR	Canada	Only up to 1 prior chemotherapy for metastatic disease, or prior therapy in adjuvant setting.	NR	NR
Unclear if 2nd line	Baselga, 2012	III	229	116	Spain, France, Brazil	LaBC or MBC, prior anthracycline and/or taxane in adjuvant or metastatic setting, max of 1 chemotherapy regimen in metastatic	100% HER2–	PFS

Line of therapy within metastatic setting	First author, year	Phase	N	2nd line subgroup size	Location	Enrolment criteria	HER2 status	Primary endpoint
						setting. (1st or 2nd line [45–57% 2nd line] overall in trial). [Note: reporting is not clear whether 2nd line relates to chemotherapy overall or to setting in metastatic disease]		
	Sato, 2012 (abstract)	III	163	N/A	Japan	MBC patients previously treated with an anthracycline (though unclear if prior treatment was in adjuvant or metastatic setting from this abstract).	100% HER2–	PFS
	Ahmad, 2013	II	72	N/A	India	MBC patients who have failed previous chemotherapy (unclear if chemotherapy was given in adjuvant or metastatic setting).	NR	ORR
2nd line or later	Keller, 2004	III	301	N/A	USA, Mexico, Europe	LaBC or MBC (stage IIIb or IV), progression on a taxane during or within 6 months of taxane therapy for advanced disease, no more than 2 chemotherapy regimens in the advanced setting (i.e. excluding adjuvant setting).	NR	PFS
	Palmieri, 2012	II	37	N/A	UK	MBC, progressive disease following anthracycline treatment (N.B. >80% were 3rd line or later).	Unselected, % NR	OS
2nd line or later (subgroup)	Gradishar, 2005	III	460	268	USA/Canada, UK, Russia/Ukraine	Mixed line enrolled (1st line, 2nd line, 3rd line, 4th line or more), 83% 1st or 2nd line, but 2nd or later line subgroup data reported separately.	NR	ORR

Abbreviations: ABC, advanced breast cancer; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; HER2+, human epidermal growth factor receptor 2-positive; HER2–, human epidermal growth factor receptor 2-negative; LaBC, locally advanced breast cancer; MBC, metastatic breast cancer; N/A, not applicable; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Table 2. Patient characteristics of RCTs investigating second- and/or later-line therapy for metastatic disease (n=14)

Line of therapy within metastatic setting	First author, year	Treatment arm	N	Median age, years	ECOG status	Race/ ethnicity of patients	Metastatic sites/organs involved, n (%†)	Any visceral disease, n (%)	Liver metastases, n (%)	Lung metastases, n (%)	ER+, n (%)	PR+, n (%)
2nd line	Gasparini, 1991	Epirubicin	25	60	NR; median KS 80	NR	1 site: 6 (27%) 2 sites: 8 (36%) ≥3 sites: 8 (36%)	9 (41%)	NR	NR	NR	NR
		Doxorubicin	24	55		NR	1 site: 7 (33%) 2 sites: 7 (33%) ≥3 sites: 7 (33%)	8 (38%)	NR	NR	NR	NR
	Dieras, 1995	PTX 175 q3w	41	52	0: 39%; 1: 51% 2: 10%	NR	NR	33 (80%)	24 (59%)	14 (34%)	NR	NR
		Mitomycin	40	52.5	0: 45%; 1: 40%; 2: 15%	NR	NR	38 (95%)	24 (60%)	18 (45%)	NR	NR
	Venturino, 2000	Vinorelbine	33	62.5	Median 0 (range 0–1)	NR	NR	19 (58%)	NR	NR	14 (42%)	10 (30%)
		Leucovorin then 5-FU	33	60.0	Median 0 (range 0–2)	NR	NR	23 (70%)	NR	NR	10 (30%)	8 (24%)
		Mitoxantrone + leucovorin then 5-FU	33	60.5	Median 1 (range 0–2)	NR	NR	22 (67%)	NR	NR	11 (33%)	10 (30%)
	Papadimitriou, 2009	DTX 40 weekly	34	57	0: 71%; 1: 21%; 2: 9%	NR	NR	NR	19 (56%)	14 (41%)	ER and PR positive: 25 (74%)	
		DTX 35 weekly + GEM	41	57	0: 56%; 1: 37%; 2: 7%	NR	NR	NR	21 (51%)	17 (42%)	ER and PR positive: 27 (66%)	

Line of therapy within metastatic setting	First author, year	Treatment arm	N	Median age, years	ECOG status	Race/ ethnicity of patients	Metastatic sites/organs involved, n (%†)	Any visceral disease, n (%)	Liver metastases, n (%)	Lung metastases, n (%)	ER+, n (%)	PR+, n (%)
	Von Minckwitz, 2014/TANIA	Bevacizumab + chemotherapy	247	56	0–2	NR but mainly Europe	≥3 sites: 80 (32%)	186 (75%)	143 (58%)	70 (28%)	ER+ and/or PR+: 198 (80%)	
		Single-agent chemotherapy (investigator's choice)	247	54			≥3 sites: 88 (36%)	190 (77%)	151 (61%)	75 (30%)	ER+ and/or PR+: 188 (76%)	
Unclear if 2nd line	Sato, 2012 (abstract)	DTX 60 q3w + CAPE	82	NR	0 or 1	Japanese	NR	NR	NR	NR	NR	NR
		Sequential DTX 70 q3w until progression, followed by CAPE	81	NR	0 or 1		NR	NR	NR	NR	NR	NR
	Ahmad, 2013	DTX 75 q3w	23	45	0–2	Asian (India)	NR	NR	NR	NR	NR	NR
		Nanosomal DTX liquid suspension (75mg/m^2) q3w	49	47	0–2		NR	NR	NR	NR	NR	NR
2nd line (subgroup)	Nielsen, 1990	Epirubicin	76	56	0–1: 76%; 2–3: 24%	NR	1 site: 38 (50%) 2 sites: 27 (36%) ≥3 sites: 11 (14%)	NR	15 (20%)	23 (30%)	ER or PR positive: 32 (42%)	

Line of therapy within metastatic setting	First author, year	Treatment arm	N	Median age, years	ECOG status	Race/ ethnicity of patients	Metastatic sites/organs involved, n (%†)	Any visceral disease, n (%)	Liver metastases, n (%)	Lung metastases, n (%)	ER+, n (%)	PR+, n (%)
		Epirubicin + vindesine	67	55	0–1: 78%; 2–3: 22%	NR	1 site: 33 (49%) 2 sites: 27 (40%) ≥3 sites: 7 (10%)	NR	13 (19%)	21 (31%)	ER or PR positive: 32 (48%)	
	Joensuu, 1998	Epirubicin then mitomycin	150	56	WHO PS 0: 19%; 1: 65% 2: 16%	NR	NR	NR	45 (29%)	39 (26%)	61 (40%)	NR
		CEF then mitomycin + vinblastine	153	55	WHO PS 0: 23%; 1: 63%; 2: 14%	NR	NR	NR	53 (35%)	43 (29%)	58 (39%)	NR
	Norris, 2000	Doxorubicin + vinorelbine	151	55	0: 24%; 1–2: 76%	NR	1 site: 30 (20%) 2 sites: 45 (30%) ≥3 sites: 76 (50%)	NR	68 (45%)	60 (40%)	85 (56%)	NR
		Doxorubicin	149	55	0: 24%; 1: 76%	NR	1 site: 28 (19%) 2 sites: 37 (25%) ≥3 sites: 84 (56%)	NR	66 (44%)	60 (40%)	74 (50%)	NR
	Baselga, 2012	Sorafenib + CAPE	115	55.1 (mean)	0: 69%; 1: 30%	White: 85.2% Black: 4.3% Mestizo*: 5.2%	NR	87 (75.7%)	NR	NR	ER+ and/or PR+: 94 (81.7%)	

Line of therapy within metastatic setting	First author, year	Treatment arm	N	Median age, years	ECOG status	Race/ ethnicity of patients	Metastatic sites/organs involved, n (%†)	Any visceral disease, n (%)	Liver metastases, n (%)	Lung metastases, n (%)	ER+, n (%)	PR+, n (%)
		Placebo + CAPE	114	54.4 (mean)	0: 68%; 1: 30%	White: 86.0% Black: 6.1% Mestizo*: 6.1%	NR	84 (73.7%)	NR	NR	ER+ and/or PR+: 79 (69.3%)	
2nd line or later	Keller, 2004	PLD	150	56.0	KS 60–70: 19% >70: 81%	NR	1 site: 52 (35%) 2 sites: 59 (39%) ≥3 sites: 39 (26%)	95 (63%)	NR	NR	71 (47%)	NR
		Vinorelbine or mitomycin C + vinblastine	151	56.0	KS 60–70: 17% >70: 83%	NR	1 site: 50 (33%) 2 sites: 47 (31%) ≥3 sites: 52 (34%)	99 (66%)	NR	NR	72 (48%)	NR
	Palmieri, 2012	DTX 100 q3w	18	45	NR	NR	NR	NR	7 (39%)	8 (44%)	ER+ and PR+: 4 (22%) ER+ and PR–: 7 (39%) ER– and PR+: 1 (5.6%)	
		Vinorelbine	19	52	NR	NR	NR	NR	4 (21%)	10 (53%)	ER+ and PR+: 3 (15.8%) ER+ and PR–: 6 (31.6%) ER– and PR+: 2 (10.5%)	

Line of therapy within metastatic setting	First author, year	Treatment arm	N	Median age, years	ECOG status	Race/ ethnicity of patients	Metastatic sites/organs involved, n (%†)	Any visceral disease, n (%)	Liver metastases, n (%)	Lung metastases, n (%)	ER+, n (%)	PR+, n (%)
2nd line or later (subgroup)	Gradishar, 2005	Nab-PTX 260 q3w	229	53.1 (mean)	0: 35%; 1: 59% 2–3: 6%	White: 97% Black: <1% Hispanic: 1% S. Asian: 0.9% Asian: <1% Other: <1%	1 lesion: 3% 2–3 lesions: 18% >3 lesions: 79%	176 (76%)	92 (40%)	74 (32%)	NR	NR
		PTX 175 q3w	225	53.3 (mean)	0: 36%; 1: 61%; 2–3: 2%	White: 97% Black: 2% Hispanic: <1% S. Asian: 0% Asian: 0% Other: 0%	1 lesion: 4% 2–3 lesions: 24% >3 lesions: 72%	182 (81%)	97 (43%)	79 (35%)	NR	NR

Abbreviations: CAPE, capecitabine; CEF, cyclophosphamide, epirubicin and 5-fluorouracil; DTX, docetaxel; ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; FU, fluorouracil; GEM, gemcitabine; KS, Karnovsky Score; NR, not reported; PLD, pegylated liposomal doxorubicin; PR, progesterone receptor; PS, performance status; PTX, paclitaxel; q3w, three-weekly; WHO, World Health Organization.

*A person of mixed European and Native American ancestry

†May not total 100%, due to either the effect of rounding or reported missing patient data within an RCT.

Table 3: Overall survival in second- and/or later-line setting

Line of therapy within metastatic setting	First author, year	Treatment arms	N	Median OS, months (95% CIs)	HR (95% CIs), p-value
2nd line	Gasparini, 1991	Epirubicin	22	12	–
		Doxorubicin	21	11	
	Dieras, 1995	Paclitaxel 175 mg/m^2, q3w	41	12.7	p=0.15
		Mitomycin	40	8.4	
	Venturino, 2000	Vinorelbine	33	9.5	–
		Leucovorin then 5-fluorouracil	33	9	
		Mitoxantrone + leucovorin then 5-fluorouracil	33	9	
	Papadimitriou, 2009	DTX weekly	34	28 (15.7, 40.3)	p=0.41
		DTX + gemcitabine	41	14 (3, 25)	
	Von Minckwitz, 2014/TANIA	Bevacizumab + chemotherapy	247	NR: OS data immature, data to be reported in future publication	
		Single-agent chemotherapy (investigator's choice)	247		
2nd line (subgroup)	Nielsen, 1990	Epirubicin	42	12	–
		Epirubicin + vindesine	33	12	
	Joensuu, 1998	Epirubicin then mitomycin	74	10	Non-significant
		CEF then mitomycin + vinblastine	88	8	
	Norris, 2000	Doxorubicin + vinorelbine	NR	9.4	–
		Doxorubicin	NR	11.3	
Unclear if 2nd line	Baselga, 2012	CAPE + sorafenib	65	19	1.08 (0.65, 1.78)
		CAPE + placebo	51	23.4	
	Sato, 2012	DTX 60 q3w + CAPE	82	NR. OS data immature	
		Sequential DTX 70 q3w until progression, then CAPE	81		

Line of therapy within metastatic setting	First author, year	Treatment arms	N	Median OS, months (95% CIs)	HR (95% CIs), p-value
2nd line or later	Keller, 2004	Pegylated liposomal doxorubicin	150	10.4	1.07 (0.79, 1.45), p=0.57
		Control: vinorelbine OR mitomycin C + vinblastine	151	9	
	Palmieri, 2012	DTX q3w	16	7.8 (4.8, 11)††	p=0.388
		Vinorelbine	18	4.9 (3.9, 5.8)††	
2nd line or later (subgroup)	Gradishar, 2005	ABI-007 (nab-paclitaxel)	131	13.0††	0.73, p=0.024
		Paclitaxel 175 mg/m^2, 3 weekly	136	10.7††	

Abbreviations: CAPE, capecitabine; CEF, cyclophosphamide, epirubicin and 5-fluorouracil; CI, confidence interval; DTX, docetaxel; HR, hazard ratio; NR, not reported; OS, overall survival; q3w, three-weekly.
††Calculated (converted from weeks to months)
N.B. OS data not reported in Ahmad 2013

Table 4. Median OS (months) in second- and/or later-line setting

Paper	CAPE	VIN	PTX 3-weekly	Nab-PTX	DTX 3-weekly	DTX weekly	Epirubicin	Epirubicin then mitomycin C	DOX	PLD	Mitomycin	CAPE + sorafenib	Epirubicin + vindesine	GEM+DTX	VIN+DOX	FEC then mitomycin + vinblastine	VIN or mitomycin C + vinblastine	5-FU+Leu	5-FU+Leu+mitoxantrone
Nielsen 1990							12						12						
Gasparini 1991							12		11										
Dieras 1995			12.7								8.4								
Joensuu 1998*								10								8			
Venturino 2000		9.5																9	9
Norris 2000									11.3						9.4				
Keller 2004										10.4							9		
Gradishar 2005†			10.7	**13**															
Papadimitriou 2009						28								14					
Baselga et al. 2012§	23.4											19							
Palmieri 2012**		4.9			7.8														

Abbreviations: CAPE, capecitabine; VIN, vinorelbine; PTX, paclitaxel; DTX, docetaxel; DOX, doxorubicin; PLD, pegylated liposomal doxorubicin; GEM, gemcitabine; FEC, fluorouracil, epirubicin and cyclophosphamide; PTX, paclitaxel; 5-FU, 5-flourouracil; Leu, leucovorin

*10 month OS value calculated (from value in weeks reported in paper)

†13 month OS value calculated (from value in weeks reported in paper). OS is statistically significantly longer with Nab-PTX vs standard PTX 3-weekly.

§Unclear line of therapy. Reportedly second line but unclear whether first line was in adjuvant and/or metastatic setting.

**Over 80% of patients were third- or later-line

N.B. No OS data was reported in Ahmad 2013. OS data was immature and so not reported yet in Sato 2012 and in von Minckwitz 2014/TANIA.

Table 5. Grade 3+ toxicities, withdrawal & safety summary in second- and/or later-line setting

Line of therapy within metastatic setting	First Author Year	Treatment arms	N‡	Key grade III/IV toxicities (%)	Withdrawals due to AEs	Summary of safety
2nd line	Gasparini 1991	Epirubicin	22	Leukopenia 0% Thrombocytopenia 0%	NR	Considering all grade AEs leukopenia and thrombocytopenia significantly more frequent on doxorubicin. Significantly greater frequency of dose delays due to haematological AEs with doxorubicin.
		Doxorubicin	21	Leukopenia 5% (1 patient, grade III) Thrombocytopenia 0%	NR	
	Dieras 1995	Paclitaxel 175 mg/m^2 q3w	41	Neutropenia 61% Peripheral neuropathy 11% Thrombocytopenia 3%	4 patients due to peripheral neuropathy	Neutropenia & peripheral neuropathy more frequent on PTX but patients received more courses of PTX than mitomycin. Thrombocytopenia more common with mitomycin. Febrile neutropenia occurred in 1 patient (3%) on PTX
		Mitomycin	40	Neutropenia 3% Neuropathy 0% Thrombocytopenia 20%	1 patient due to persistent neutropenia	
	Venturino 2000	Vinorelbine	33	Anaemia 3% Leukopenia 18% Thrombocytopenia 0% Diarrhoea 0% Paralitic ileus 3% Any grade III AE 27%	NR	Lower incidence of grade III/IV toxicities in mitoxantrone combination arm. Authors consider that it is not always the single agent therapy that is best tolerated and that analysis of QoL, pain and symptom control (nausea, fatigue, improvement in performance status) is needed in trials in patients with incurable cancers, and comparison with best supportive care.
		Leucovorin then 5-fluorouracil	33	Anaemia 0% Leukopenia 3% Thrombocytopenia 0% Diarrhoea 12% Paralitic ileus 0% Any grade III AE 15%	NR	
		Mitoxantrone + leucovorin then 5-fluorouracil	33	Anaemia 0% Leukopenia 3% Thrombocytopenia 3% Diarrhoea 0% Paralitic ileus 0% Any grade III AE 18%	NR	

Line of therapy within metastatic setting	First Author Year	Treatment arms	N‡	Key grade III/IV toxicities (%)	Withdrawals due to AEs	Summary of safety
	Papadimitriou 2009	Docetaxel 40 mg/m^2 weekly	30	Anaemia 0% Neutropenia 3% Thrombocytopenia 3% Leukopenia 10% Stomatitis 10% Diarrhoea 3% Alopecia 13% Any grade III/IV AE 3%	NR	Higher frequency of grade III/IV neutropenia with DTX+GEM (23%) vs DTX (3%) (p=0.035). Such patients received G-CSF. Grade I or II febrile neutropenia occurred in 41% with DTX+GEM vs 23% with DTX.
		Docetaxel 35 mg/m^2 + gemcitabine	39	Anaemia 5% Neutropenia 23% Thrombocytopenia 6% Leukopenia 18% Stomatitis 3% Diarrhoea 0% Alopecia 23% Any grade III/IV AE 23%	NR	
	Von Minckwitz 2014/TANIA	Bevacizumab + chemotherapy	245	Any grade III/IV AE 59% Grade III hypertension 13% Proteinuria 7%	18% discontinued BEV, mostly for proteinuria, venous embolism and pulmonary embolism 16% discontinued chemotherapy	Grade III/IV AEs more common with combination treatment, mainly due to higher frequency of grade III hypertension and proteinuria AE leading to chemotherapy discontinuation in >2% of patients was hand-foot syndrome in BEV+chemotherapy group, all of whom were receiving capecitabine
		Single-agent chemotherapy (investigator's choice)	238	Any grade III/IV AE 46% Grade III hypertension 7% Proteinuria <1%	8% discontinued chemotherapy	
2nd line (subgroup)	Nielsen 1990	Epirubicin	42	NR for subgroup	NR for subgroup	NR for subgroup but overall: thrombocytopenia significantly less frequent on epirubicin plus vindesine vs epirubicin monotherapy (p<0.01); mild-moderate peripheral neuropathy occurred in 40% of
		Epirubicin + vindesine	33			

Line of therapy within metastatic setting	First Author Year	Treatment arms	N‡	Key grade III/IV toxicities (%)	Withdrawals due to AEs	Summary of safety
						patients on combination therapy; 9 patients on epirubicin & 6 on combination had febrile neutropenia. CHF occurred in on epatient with cumulative dose of epirubicin <1000 mg/m^2 and 7/15 patients with >1000 mg/m^2; 4 patients died from CHF.
	Joensuu 1998	Epirubicin (1st line) then mitomycin (2nd line)	74	NR for 2nd line subgroup	8 patients discontinued M (12%)	Significantly greater frequency of toxicity with mitomycin + vinblastine vs mitomycin single-agent therapy, due to more leukopenia (p=0.005), nausea or vomiting (p=0.01), alopecia (p=0.003) and tendency for more anaemia (p=0.07). No difference in frequency of thrombocytopenia (p=0.28)
		CEF (1st line) then mitomycin + vinblastine (2nd line)	88	NR for 2nd line subgroup	17 patients discontinued MV (20%)	
	Norris 2000	Doxorubicin + vinorelbine	NR	NR for subgroup	NR for subgroup	NR for subgroup. However, in the overall population greater incidences of Grade 3/4 neurotoxicity, mild venous toxicity and febrile neutropenia were observed in the doxorubicin + vinorelbine arm. 11% of patients in combination arm discontinued vs. 4% in monotherapy arm.
		Doxorubicin	NR	NR for subgroup	NR for subgroup	
Unclear if 2nd line	Baselga 2012	Capecitabine + sorafenib	65	HFSR/HFS 44% (Grade III)	20% discontinued, mainly due to HFSR/HFS (9 patients) and diarrhoea (1 patient)	Grade III/IV HFSR/HFS occurred significantly more frequently with sorafenib than with placebo. With all grade HFSR/HFS it also occurred earlier with sorafenib (median 14 days to first occurrence vs 64 days) HFSR/HFS potentially impacts QoL and treatment changes. Other grade III/IV events occurred with similar frequency in treatment arms. All grade AEs were numerically higher with
		Capecitabine + placebo	51	HFSR/HFS 14% (Grade III)	9% discontinued, mainly due to HFSR/HFS (4 patients) and diarrhoea (3 patients)	

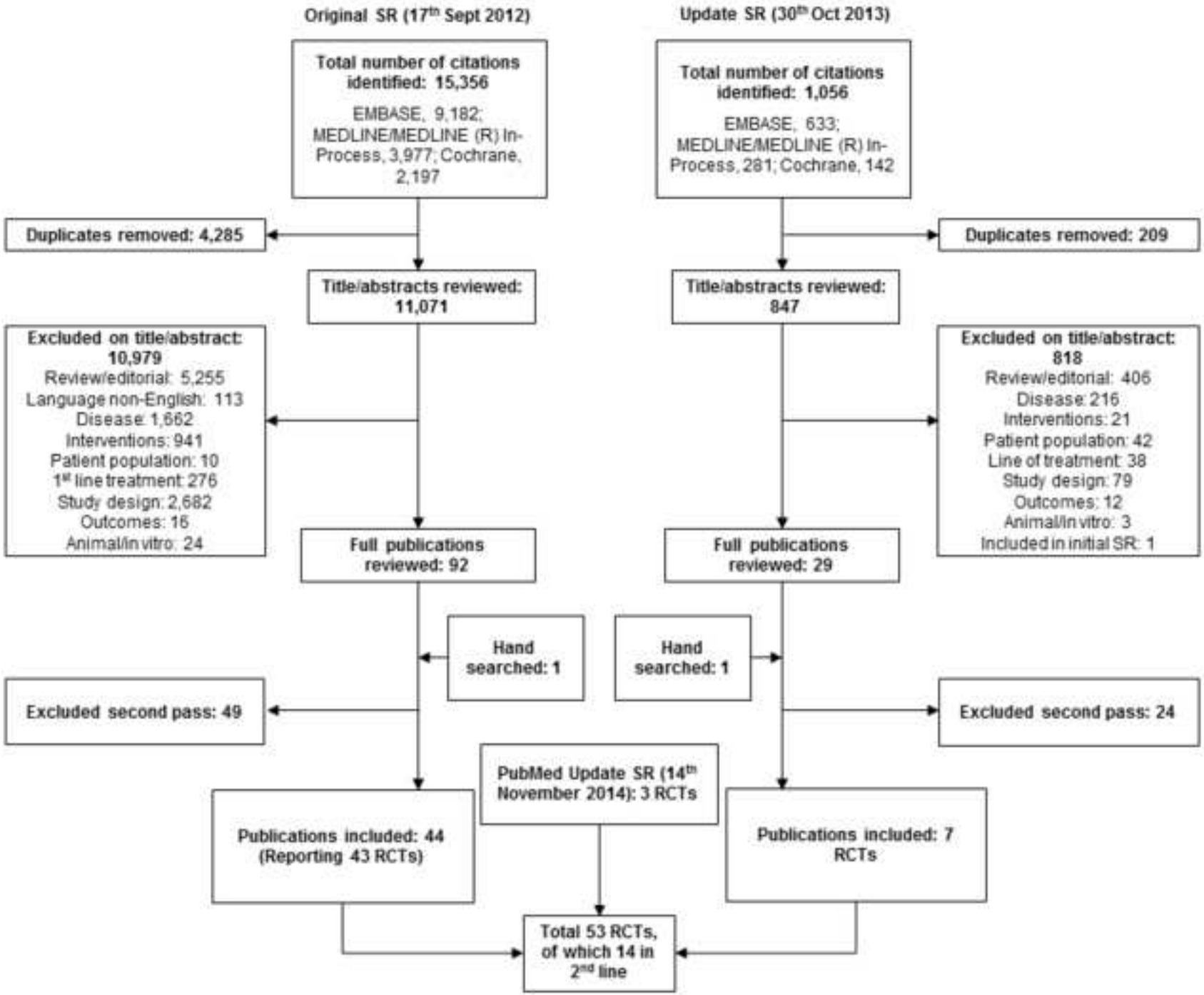
Line of therapy within metastatic setting	First Author Year	Treatment arms	N‡	Key grade III/IV toxicities (%)	Withdrawals due to AEs	Summary of safety
						sorafenib for diarrhoea, mucosal inflammation, rash, neutropenia, hypertension and HFSR/HFS. Dose delays and reductions to manage toxicities more frequent with sorafenib.
	Sato 2012	DTX 60 3-weekly + CAPE	82	Decreased neutrophil count 57.3% Neutropenia 8.5% Febrile neutropenia 6.1%	NR	ADRs with at least 5% difference in frequency were HFS (7.3% vs. 0%), fatigue (2.4% vs. 8.8%) and peripheral edema (1.2% vs. 6.3%) in the concurrent vs. sequential groups.
		Sequential DTX 70 3-weekly until progression, then CAPE	81	Decreased neutrophil count 60.0% Neutropenia 12.5% Febrile neutropenia 10.0%	NR	
2nd line or later	Keller 2004	Pegylated liposomal doxorubicin 50 mg/m^2 q4w	150	Leukopenia 20% Neutropenia 2% Febrile neutropenia 0 patients PPE 18% grade III, 1 patient grade IV LVEF changes consistent with cardiac toxicity in 22 patients	4 discontinued due to LVEF changes	Myelosuppression was lower with PLD: grade III/IV leukopenia less frequent with PLD than with control group, and grade III/IV neutropenia less frequent with PLD than with vinorelbine. Most common ADR with PLD was palmar-plantar erythrodysesthesia (37% any grade). Infusion reactions and any grade stomatitis were more common with PLD.
		Control: vinorelbine	151	Leukopenia 54% Neutropenia 8% Febrile neutropenia 2 patients	Unclear	
		Control: mitomycin C + vinblastine		Leukopenia 30% Febrile neutropenia 0 patients	Unclear	
	Palmieri 2012	Docetaxel 100 mg/m^2 q3w	18	Grade III/IV AEs 27 events Grade III/IV haematological AEs and infections 20 events	High rate of discontinuation or interruption of treatment (% unspecified)	Grade III/IV toxicity (in particular haematological AEs and infections) more frequent with DTX than with vinorelbine.
		Vinorelbine 25 mg/m^2 q2w	18	Grade III/IV AEs 4 events Grade III/IV haematological AEs and		

Line of therapy within metastatic setting	First Author Year	Treatment arms	N‡	Key grade III/IV toxicities (%)	Withdrawals due to AEs	Summary of safety
				infections 2 events		
2nd line or later (subgroup)	Gradishar 2005	ABI-007 (nab-paclitaxel)	131	NR for subgroup	NR for subgroup	Subgroup analyses reported showed that safety profiles of 1st line patients similar to those of 1st and 2nd/later line overall population. Treatment-related grade IV neutropenia significantly lower on nab-paclitaxel (9%) than on standard paclitaxel (22%), p<0.001, enabling the dose to be increased by 50%. Febrile neutropenia <2% in both arms. Grade III sensory neuropathy 10% with nab-paclitaxel vs. 2% with standard paclitaxel, but easily managed with dose interruption or reduction. No grade III/IV hypersensitivity reactions to nab-paclitaxel (in spite of no premedication) whereas they did occur with standard paclitaxel despite premedication. AE-related discontinuations, dose reductions and dose delays were low frequency in both arms (3% with nab-paclitaxel and 7% on standard paclitaxel).
		Paclitaxel 175 mg/m^2 q3w	136	NR for subgroup	NR for subgroup	

ADR, adverse drug reaction (treatment-related adverse event); CEF, cyclophosphamide, epirubicin and fluorouracil; CR, complete response; ER, estrogen receptor; M, mitomycin; MV, mitomycin + vinblastine; NR, not reported; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, progesterone receptor; PRe, partial response; QoL, quality of life; SD, stable disease; TTP, time to progression

†May not total 100%, due to either the effect of rounding or reported missing patient data within an RCT.

††Calculated (converted from weeks to months)



Highlights:

- Line of therapy terminology is imprecise
- Median OS from second-line MBC estimated from larger trials is 8–13 months
- Only one RCT has shown significant efficacy benefit alongside favourable safety
- As single agent, nab-paclitaxel has demonstrated significant OS benefit.
- QoL data and precise OS estimation are needed according to patient characteristics